**Amendments to the Drawings:**

The attached sheet of drawings include an amendment to sheet 6 of 6 to include the figure number at the bottom of the page to show as Fig. 5. This sheet, which includes Fig. 5 replaces the original sheet 6 of 6 of the drawings.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

## REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 110-127 will be pending in this application and are presented for examination. Claims 110-111, 113, 116-117, 119, 121, 124 and 126-127 have been amended. Support for the amendment to claims 110-111 is found, for example, on page 16, lines 6-10; on page 40, line 19 through page 41 line 8. Support for the amendment to claim 116-117 and 126-127 is found, for example, on page 46, lines 26-32; and on page 53, lines 7-12. No new matter has been introduced. Reconsideration of the rejected claims is respectfully requested.

### I. Priority

The Examiner has denied the priority claims to application 09/054,830 field on April 3, 1998 and alleged that the 09/054,830 application does not disclose the nearest-neighbor methods for calculation of melting temperatures or duplex stability. Priority claims for the present application is granted to application 09/724,959 filed on November 28, 2000. Applicants do not acquiesce with the Examiner, however, in the interest of furthering the prosecution, Applicants will respond the cited prior art references having a reference date after the April 3, 1998 filing date of application 09/054,830, but before the November 28, 2000 filing date of application 09/724,959.

### II. Drawings

The drawings have been objected to as allegedly failing to comply with 37 CFR §1.84(p)(5) for not including the reference sign mentioned in the description. In response, Applicants have included the label "Fig. 5" in the drawing sheet marked with 6 of 6 and submitted with this amendment a replacement sheet as well as an annotated sheet showing the changes. Accordingly, the objection to drawings has been overcome. Applicants respectfully request that this objection be withdrawn.

## III. Specification

The specification has been objected to for not using capitalized letters for trademarks. In response, Applicants have revised the paragraphs with the trademarks being presented in capital letters. As such, Applicants respectfully request the withdrawal of the objection.

The abstract has been objected to for not including the claimed subject matter. In response, Applicants provide an abstract directed to the claimed subject matter. Accordingly, Applicants respectfully request the present objection be withdrawn.

## IV. Claim Rejections under 35 U.S.C. §101

Claims 110-123 and 125-127 stand rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter. The Examiner alleges that the instant claims are drawn to computational means and do not produce a real-world result. In response, Applicants have amended independent claims 110 and 111, and respectfully request reconsideration in view of the remarks below.

With regard to the requirement of a "tangible result," the Interim Guidelines state that "the claim must set forth a practical application of that §101 judicial exception to produce a real-world result." (Guidelines, p. 21). The Guidelines cite *Corning v. Burden*, 56 U.S. (15 How.) 252, 268 (1854), in noting that "it is for the discovery or invention of some practical method or means of producing a beneficial result or effect, that a patent is granted . . ." (Guidelines, p. 21-22).

Applicants submit that claims 110-123 and 125-127 produce "real-world results." Claims 110-123 and 125-127 recite methods of designing an oligonucleotide sequence having a selected duplex stability by calculating duplex stability and melting temperatures of an oligonucleotide having at least one modified base using a nearest-neighbor model. More particularly, the present invention provides a method of designing an oligonucleotide sequence (with a modified base) that will be useful for temperature or denaturing gradient gel electrophoreses, southern blotting or hybridization probe assays (see, abstract in *Biotechniques*, 27:1218-1224, 1999; reference No. 54, IDS filed). The result of the claimed methods is the

output of a sequence having the selected duplex stability. The calculation of the duplex stability and melting temperature to output a sequence with the selected duplex stability is a "real-world result," useful for designing probes for enhanced mismatch discrimination, better hybridization assays and PCR reaction conditions. Thus, Applicants respectfully submit that claims 110-123 and 125-127, as amended, achieve a "tangible result."

The Examiner further asserts that the methods as claimed may operate entirely within the confines of a computer or a human mind without any communication to the outside world. The Examiner appears to have rejected claims 110-123 and 125-127 because the claims do not recite performance of a result outside a computer.

In *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, the Federal Circuit applied the "useful, concrete, and tangible result" test in determining whether claim 1 of U.S. Patent No. 5,193,056 is directed to statutory subject matter. *See* 47 USPQ2d at 1602. The Federal Circuit held: the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"-a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades. *See*, 47 USPQ2d 1596, 1602 (Fed. Cir. 1998).

As such, the case law does not require that a claim directed to the statutory subject matter must include performance of a result outside of a computer, or any physical transformation outside of the computer. In contrast, a claim is statutory so long as it produces "a useful, concrete and tangible result." *See* State Street, 149 F.3d at 1374, 47 USPQ2d at 1602. Hence, a claim can be patentable even if the claim does not include a result outside of a computer or any physical transformation outside of the computer.

In view of the above, the claimed methods are useful, concrete and tangible. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn.

## V. Claim Rejections under 35 U.S.C. §112

Claims 110-127 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. To the extent that the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Claims 110 and 111 have been amended to provide a proper antecedent basis for the term "N-1 neighboring base pairs". Claim 113 has been amended such that the trademark GENBANK is directed to the source not to the product. Claims 117 and 126-127 have been amended to recite the term "enhanced ability of" and to more clearly define the claimed invention. Applicants believe that the term "enhanced ability of" meets the standard set forth in *In Ex parte Anderson*, 21 U.S.P.Q.2d 1241 (B.P.A.I. 1991) for the reasons set forth below.

In *Anderson*, the Board held that the term "superior" was indefinite because one was left to surmise and conjecture to determine the specific properties to be compared and how comparable their values need be. Therefore, the Board recommended that the specification provide some limited guidance for the term as to ***what is being compared and the level of superiority being disclosed*** (see, *Anderson*, at 1250).

Here, the term "enhanced ability of" has been clearly described in the specification and used to compare the mismatch discrimination ability of the oligonucleotide having modified bases with those having unmodified bases. For example, on page 53, lines 7-12, the specification discloses that MGB-modified oligonucleotide conjugates allow discrimination between a perfect hybrid and a hybrid containing a single-base mismatch. As such, the conjugates are useful in hydrolyzable probe assays for the identification of single-nucleotide polymorphisms and the like. The specification further illustrates the level of the enhancement for mismatch discrimination using oligonucleotides having at least one modified base as compared to oligonucleotides having only unmodified bases (see, Fig. 3). For instance, a short 15-mer probe oligonucleotide having a modified base exhibits better mismatch discrimination than the probe having an unmodified base (see, Fig. 3 and Example 9). As such, the term "enhanced ability of" is definite.

In view of the amendment and comments above, Applicants submit that claims 110-127 are definite within the meaning of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

## VI. Claim rejections under 35 U.S.C. §102

### A. Rejection under §102(b) over Griffin *et al.*

Claims 110-111, 114-115, 117, 123, and 126 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Griffin *et al.* (*Analytical Biochemistry*, Vol. 260, pages 56-63, 1998; hereinafter "Griffin"). Applicants respectively traverse the rejection.

As set forth in MPEP 2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

Applicants assert that Griffin does not teach each and every element of the claimed invention. Griffin discloses a method for predicting the stability of peptide nucleic acid (PNA):DNA duplexes using nearest neighbor models, wherein the duplexes have ***unmodified natural bases*** (see, page 56, column 2, third paragraph and page 57, column 1, third paragraph of Griffin). Griffin fails to disclose or suggest a method for designing an oligonucleotide, wherein at least one base is a modified base selected from the group of universal bases, unsubstituted and 3-substituted pyrazolo[3,4-d]pyrimidines and 5-substituted pyrimidines. Independent claim 111 recites an additional element wherein the oligonucleotide comprises a minor grove binder (MGB). Therefore, Griffin fails to teach each and every element of independent claims 110 and 111, or the claims depending from claims 110 and 111. Accordingly, Applicants respectfully request that the rejection of claims 110-111, 114-115, 117, 123, and 126 under 35 U.S.C. §102(b) be withdrawn.

### B. Rejection under §102(e) over Lizardi *et al.*

Claims 110 and 125 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Lizardi *et al.* (U.S. Pat. No. 6,403,319; hereinafter "Lizardi"). Applicants respectfully traverse the rejection.

Applicants assert that Lizardi does not anticipate the claimed invention, because Lizardi fails to teach each and every element of the claimed invention. Claims 110 and 125 as amended, recite a method of designing an oligonucleotide sequence having at least one modified base. The present invention applies nearest-neighbor (NN) ***thermodynamic parameters involving modified bases***. In contrast, Lizardi does not teach NN thermodynamic parameters involving at least one modified base. Lizardi discloses capture probes that can contain modified nucleotides and further notes that the probes are capable of forming duplexes with other nucleic acids. Lizardi further discloses that the duplex stability of the probes can be calculated using nearest-neighbor models according to methods described in the cited Santa Lucia reference. However, the Santa Lucia reference ***does not*** teach the NN thermodynamic parameters involving oligonucleotides with ***modified bases*** as recited in the claimed invention. The Santa Lucia reference describes the comparison of DNA nearest-neighbor (NN) $G°_{37}$ parameters for polymer and oligonucleotide duplexes from seven laboratories, and the derivation of a unified set of parameters for the description of polymer and oligomer thermodynamics. The NN free energy parameters for 10 possible dimer duplexes are presented, along with additional parameters for differences between terminal and internal NNs and for duplexes arising from self-complementary sequences. All the NN thermodynamic parameters described therein are directed to oligonucleotides having ***unmodified bases***. There is absolutely ***no*** description of NN thermodynamic parameters involving ***modified bases*** in the Santa Lucia reference. Therefore, Lizardi fails to teach each and every element of the claimed invention and claims 110 and 125 are not anticipated by Lizardi. Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

C. Rejection under §102(e) over Lokhov *et al.*

Claims 110-113 and 118-122 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Lokhov et al. (U.S. Pat. Publication No. 2003/0235822; hereinafter "Lokhov"). Applicants respectfully traverse the rejection.

As set forth in 35 U.S.C. §102(e)(1): a person shall be entitled to a patent unless the invention was described in an application for patent, published under section 122(b), by another filed in the United States ***before*** the invention by the applicant for patent.

Lokhov has a priority date of November 28, 2000, which is the same as the alleged effective filing date of the present invention. Since Lokhov does not have an effective filing date ***before*** the invention by the Applicants, Lokhov does not meet the statutory requirement of being a valid 102(e) prior art. Accordingly, Applicants respectfully request that the rejection of claims 110-113 and 118-122 under 35 U.S.C. §102(e) be withdrawn.

D. Rejection under §102(f) over Lokhov *et al.*

Claims 110-113 and 118-122 have been rejected under 35 U.S.C. 102(f) as allegedly not being invented by Applicants. The Examiner alleges that the claims of the instant application are obvious variations of claims 1-2, 7-9 and 24-25 of the copending Application 10/176,972, and the instant application has a different inventive entity from the copending Application 10/176,972. In response, Applicants submit herewith a Rule 1.132 declaration signed by all the inventors of the present invention. In view of the declaration, Applicants believe that the rejection is overcome and respectfully request that the rejection under 35 U.S.C. §102(f) be withdrawn.

## VII. Claim Rejections under 35 U.S.C. §103

A. Schutz *et al.* in view of Kutyavin *et al.*

Claims 110-114 and 117-124 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Schutz et al. (*Biotechniques*, Vol 27, 1218-1224, 1999; hereinafter "Schutz") in view of Kutyavin et al (*Nucleic Acids Research*, Vol 28, 655-661, 2000; hereinafter "Kutyavin"). Schutz is relied on by the Examiner as allegedly describing a software for predicting the stability of an oligonucleotide duplex, such as calculating a melting temperature ($T_m$). Kutyavin is relied on by the Examiner as allegedly teaching the calculation of the thermodynamic parameters for an identified sequence that includes at least one modified base. The Examiner takes the position that it would have been obvious to a person of skill in the art to

use Schutz's program with the method of Kutyavin to arrive at the presently claimed invention. Applicants respectfully traverse the rejection.

As set forth in MPEP §2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success.

Applicants submit that the cited prior art references do not teach all the limitations of the claimed invention. Schutz teaches a computer program for calculating the $T_m$ of oligonucleotide DNA duplexes on the basis of nearest-neighbor thermodynamic parameters, which include enthalpy, entropy and free energies. Schutz ***does not*** teach NN thermodynamic parameters involving ***modified bases***, and does not provide any indication of how to develop those parameters for modified bases as recited in independent claims 110 and 111 of the present invention. Kutyavin fails to supply the teachings that are clearly lacking in Schutz. Kutyavin describes the synthesis of DNA probes with conjugated minor group binder (MGB), formation of DNA duplex and determination of the melting temperatures by UV melting studies (see, abstract; page 655, right column, first paragraph; pages 655-656, Materials and Methods; and Figures 2, 6-8 and 10). Kutyavin also teaches the calculation of $\Delta\Delta G^\circ$ of each type of the ***entire*** duplex at 50 °C (see, page 656, right column, lines 1-13; and Figure 3). There is ***absolutely no teaching or suggestion*** anywhere in Kutyavin regarding NN thermodynamic parameters involving modified bases as recited in the claimed invention. Accordingly, Schutz or Kutyavin alone or in combination do not teach all the claim limitations.

Moreover, Applicants assert that the invention is not obvious because the Schutz reference only provides an invitation to explore. In *Ex parte Obukowicz*, the Board held that [T]he specific statement by Dean (prior art reference) is ***not*** a suggestion to insert the gene into the chromosome of bacteria and apply that bacteria to the plant environment in order to protect the plant. At best, the Dean statement is but ***an invitation to scientists to explore*** a new technology that seems a promising field of experimentation. The Dean statement is of the type

that gives ***only general guidance*** and is not at all specific as to the particular form of the claimed invention and ***how to achieve*** it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious (see, *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063, 1035 (B.P.A.I. 1992) citing *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988)).

Schutz states that "...the application of the program ... is of special interest when selecting a probe/anchor pair that gives the best discrimination (difference in $T_m$ between wild-type and mutation)" (see, page 1222, right column, lines 7-10). Like in *Ex parte Obukowicz* and *In re O'Farrell,* the statement in Schutz is ***not*** a suggestion to apply the program to predict the duplex stability of an oligonucleotide having modified bases. Schutz provides only an ***invitation to explore*** another new technology. Moreover, the statement gives only general guidance. For example, the statement "probe/anchor pair that gives the best discrimination" is not at all focused on the claimed invention or specific to the particular form of the claimed invention, such as oligonucleotides having modified bases and optionally minor groove binders. Therefore, under *In re O'Farrell*, the statement in Schutz can only be an invitation of "obvious to try", but it ***does not*** make the present claimed invention obvious.

In view of the above, Applicants submit that a *prima facie* case of obviousness has not been set forth by the Examiner and respectfully request that the rejection of claims 110-114 and 117-124 under 35 U.S.C. §103(a) be withdrawn.

B. Schutz *et al.* in view of Singh et *al.*

Claims 110-114, 116-117, 123-124 and 127 also stand rejected under 35 U.S.C. 103(a) as allegedly being obvious over Schutz in view of Singh *et al.* (*Chem Comm.* 455, 1998; hereinafter "Singh"). Applicants respectfully traverse the rejection.

Applicants assert that the cited prior references do not teach all the claim limitations. As discussed above, Schutz teaches a computer program for calculating the $T_m$ of oligonucleotide DNA duplexes on the basis of nearest-neighbor thermodynamic parameters. Schutz ***does not*** teach NN ***thermodynamic parameters involving modified bases***. Singh fails to supply the teachings that are clearly lacking in Schutz. Singh teaches the synthesis of locked nuclei acids (LNA) and determination of $T_m$ for the duplexes formed between LNA and DNA or

RNA. The locked nucleic acids in Singh all have ***unmodified bases***. Singh in no instance teaches or suggests LNA having a modified base as recited in the presently claimed invention. Moreover, there is absolutely no description in Singh regarding NN ***thermodynamic parameters involving modified bases***. Accordingly, Schutz or Singh alone or in combination fail to teach all the claim elements. Accordingly, Applicants respectfully request that the rejection of claims 110-114, 116-117, 123-124 and 127 under 35 U.S.C. §103(a) be withdrawn.

### VIII. Double Patenting

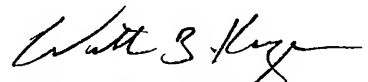
Claims 110-113 and 118-122 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1-2, 6-9, and 24-25 of copending Application No. 10/176,972. Applicants respectfully request that this provisional rejection be held in abeyance until the present subject matter is found allowable. Should the Examiner feel that the amended claims remain subject to the provisional rejection, Applicants will file a terminal disclaimer.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5015.

Respectfully submitted,



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